(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 717 986 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
13.09.2000 Bulletin 2000/37

(51) Int Cl.[7]: **A61K 9/00**

(21) Application number: **95309191.5**

(22) Date of filing: **18.12.1995**

(54) **Rotor granulation and coating of acetaminophen, pseudoephedrine, chlorpheniramine, and, optionally, dextromethorphan**

Rotogranulat und Beschichtung von Acetaminophen, Pseudoephedrin, Chlorpheniramin und, gegebenenfalls, Dextromethorphan

Rotogranulation et enrobage d'acetaminophène, pseudoéphédrine, chlorphéniramine, et, éventuellement, dextrométhorphane

(84) Designated Contracting States:
BE DE FR GB IT

(30) Priority: **19.12.1994 US 359108**

(43) Date of publication of application:
26.06.1996 Bulletin 1996/26

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EP-A- 0 411 952
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EP-A- 0 523 847

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Description

Field of the Invention

[0001] This invention relates to chewable tablets containing more than one active medicament, maintaining good taste and mouth-feel.

Background of the Invention

[0002] Orally administered medicaments are given to the patient in many forms, such as liquid solutions, emulsions, or suspensions, or in solid form such as capsules or tablets (as used herein, the term "tablet" means any shaped and compressed solid dosage form, including caplets). Medicaments administered in tablet or capsule form are usually intended to be swallowed whole. Therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the dosage form, except for the provision of means to prevent the taste from being apparent during the short time that the dosage form is in the mouth. Such means may include the use of an appropriately thin and quickly dissolving coating on the tablet, the use of the gelatin capsule form, or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth.

[0003] It is desirable to provide the medicine either in liquid form or in a chewable solid form for children, especially toddlers, older persons, and many other persons, that have trouble swallowing whole tablets and capsules. Even where the medicine can be formulated as a liquid, it is desirable also to be able to provide a chewable solid form for convenience.

[0004] A common problem with chewable tablet forms is the often disagreeable taste of the active ingredient which manifests itself during chewing. In some cases, the taste of the active medicament in a tablet can be masked by adding flavoring ingredients to the tablet.

[0005] A different approach was taken with a children's size tablet containing acetaminophen (acetyl para-amino phenol or "APAP"). A children's size tablet of APAP is available commercially wherein the APAP is present in granules that are coated with ethyl cellulose. A significant proportion of the APAP remains shielded by the coating (and therefore does not contribute to taste) while the tablet is in the mouth, despite some breakage of the ethyl cellulose coating during compression of the tablet and some additional breakage of the coating during chewing. The APAP becomes available via permeation through the coating (although ethyl cellulose is not soluble in aqueous fluids, water does permeate through the coating) and from the granules wherein the coating was broken.

[0006] U.S. Patent No. 5,075,114 issued to Edward J. Roche on December 24, 1991, describes chewable tablets prepared by coating compressed granulated active acetaminophen, using fluidized bed coating. Combinations of two or more of pseudoephedrine HCl, chlorpheniramine maleate, dextromethorphan HBr, diphenhydramine HCl or citrate, acetaminophen, ibuprofen, and naproxen are contemplated, but it is also suggested that coatings may be varied to provide a slower release of one medicament over another, indicating discrete granules of each medicament. The coatings comprised about 5 to about 28% of the total dry weight of the granule and comprised a polymer blend.

[0007] U.S. Patent No. 5,260,072 issued to Edward J. Roche, et al. on November 9, 1993 describes rotor granulations and tastemasking coatings comprising polymer blends of one or both of cellulose acetate or cellulose acetate butyrate and polyvinylpyrrolidone. The inclusion of two or more medicaments is contemplated, but it is also indicated that the coatings for each medicament can be varied, suggesting discrete granules of each medicament.

[0008] EP-A-0 523 847 describes chewable tablets comprising rotor granules coated with polymer blends including cellulose acetate and methyl aminoethyl methacrylate neutral methacrylic acid ester (the preferred representative compound being Eudragit® E-100). The coating method described is fluid-bed coating. The inclusion of two or more medicaments is contemplated, but not described by example.

[0009] A need remains for a chewable tablet comprising more than one active ingredient without sacrificing taste. This is particularly important for children.

Summary of the Invention

[0010] In one aspect, the present invention relates to chewable tablets containing a solid analgesic and at least one other medicament which is soluble in water. The analgesic and the other medicaments(s) are granulated together with a binder to form individual granules comprising all the active ingredients. The granules are coated with a taste-masking composition. The tablet contains the coated granules, sweeteners, flavoring, and, optionally, other excipients.

[0011] In another aspect, the present invention relates to chewable tablets containing a solid analgesic and at least one other medicament which is soluble in water produced by a process by which the solid analgesic and water soluble medicament(s) are granulated together with a binder, coated with a taste-masking composition, and then blended and compressed with sweeteners, flavoring, and, optionally, other excipients.

[0012] In a further aspect, the present invention relates to a process for preparing chewable tablets containing more than one medicament. According to the process of the invention, a solid analgesic is granulated with at least one other water soluble medicament and a binder. The granules are then coated with a taste-masking composition, and blended and compressed with sweeteners, flavoring, and, optionally, other excipients.

Detailed Description

[0013] The invention will now be described specifically in terms of its most preferred embodiments. Reference will also be made in detail herein to other preferred embodiments of the compositions, processes, and methods of the invention. The tablets according to the invention are prepared by granulation of a solid analgesic with one or more water soluble active ingredients and a binder, coating the resultant actives granulation with a taste-masking composition, and then combining the coated granulation with other excipients, such as sweeteners, flavoring agents, extenders, and the like, and compressing into tablet form. The taste-masking provided by the coating helps limit the quantity of other flavoring agents and sweeteners necessary in the tablet to mask the unpleasant flavor of the medicament.

[0014] The tablets according to the invention preferably contain three active ingredients or medicaments, an analgesic, antihistamine, and decongestant, and pharmaceutically acceptable salts thereof. In addition to the foregoing, the tablets can also contain a cough suppressant, and pharmaceutically acceptable salts thereof.

[0015] In a preferred embodiment, the tablets according to the invention contain acetaminophen as the analgesic, chlorpheniramine maleate as the antihistamine, and pseudoephedrine HCl as the decongestant. In a further preferred embodiment, the tablets additionally contain dextromethorphan HBr as the cough suppressant.

[0016] Depending on whether a children's regular strength or adult strength dosage is desired, the dosage form will generally contain from about 80 to about 500 mg of acetaminophen, about 0.5 to about 2 mg of chlorpheniramine maleate, about 7.5 to about 30 mg of pseudoephedrine HCl and, optionally, about 5 to about 15 mg of dextromethorphan HBr. The dextromethorphan HBr may be used in its salt form or as a 10% (wt.) adsorbate.

[0017] The active ingredients can be granulated together using, for example, a rotor granulator. A rotor granulator produces nearly spherical granulated particles which have increased strength and resistant to breakage due to the densification of the granulation mixture as the roto granules are formed in the rotor granulator fluid bed. This resistance to breakage can be advantageous when preparing tablets containing more than one active ingredient since broken particles are smaller and irregular in shape, they may not be readily coated in subsequent coating steps. This can detract from the taste-masking purpose of coating. However, other granulating methods, such as top spray and high shear granulation, are also contemplated. The granulated particles are preferably in the size range of from about 125 to about 850 microns. Generally, particles of like size facilitate blending and provide regularity to dosage forms.

[0018] The analgesic and, optionally, the cough suppressant (both in particle form) are fluidized in the rotor granulator. Then a granulating solution containing the water soluble active(s), a binder(s), and solvent(s), generally water, alcohol or mixtures thereof, are sprayed onto the fluidized particles and then dried to form the actives granulation. The granulating solution generally comprises from about 1 to about 20% by weight of the binder. Suitable binders for use in the granulating solution include starch, pregelatinized starch, gelatin, polyvinylpyrrolidone, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, ethyl cellulose, polyacrylamides, polyvinyloxoazolidone and polyvinyl alcohols.

[0019] The granulated particles are then coated with a taste masking composition, for example, in a fluid bed rotor. Other coating methods, such as a Wurster or top spray fluid bed coating process, are also contemplated. In the tablets according to the invention, it is desirable that all particles are coated uniformly throughout the particle surface and to the same extent.

[0020] The coated particles or granules are then dried. Drying can be performed in a fluid bed rotor unit, or by other suitable means.

[0021] Granulating and coating methods are disclosed in, for example, Jones, D.M., "Factors to Consider in Fluid-Bed Processing", Pharmaceutical Technology, April 1985 and Jager, F.F., et al., "Effect of Material Motion on Agglomeration in the Rotary Fluidized-Bed Granulator," Drugs Made in Germany, Vol. XXV, pp. 61-65 (1982) (both incorporated herein by reference).

[0022] A solids taste-masking composition is generally used for coating the granulated particles. In a preferred embodiment, a combination of cellulose acetate and methylaminoethyl methacrylate neutral methacrylic acid ester (MM/MAE, i.e., Eudragit® E 100), in a ratio of 65:35, respectively, is used. Generally, the particles are coated with from about 8 to about 20 percent of the polymer, based on the total particle weight.

[0023] Other coating materials which can be utilized include polymer compositions including cellulose acetate (CA), or cellulose acetate butyrate (CAB), polyvinylpyrrolidone (PVP), cellulose triacetate powder (CAT), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and methylaminoethyl methacrylate and neutral methacrylic acid ester (MM/MAE), and mixtures thereof.

[0024] When CA or CAB is utilized, it is preferable that PVP is added to the coating mixture to provide bioavailability.

CA and CAB are quite water insoluble. The preferred ratio of CA and/or CAB to PVP is from about 95:5 to about 60:40.

[0025] Those polymer coatings which are not water soluble can be solubilized in organic solvents for use in coating. A wide variety of organic solvents can be used. For instance, acetone, methanol, methylene chloride, ethyl acetate, toluene-ethanol, and others. A suitable solvent system can be readily ascertained by one skilled in the art. The proportion of the polymer in the coating solution will generally range from about 5 to about 20% by weight.

[0026] A tablet blend is then prepared comprising the coated particles, sweetener, flavoring, and other excipients. After blending, the tablet is compressed in the presence of a lubricant (to lubricate the dye walls and punches used during the tablet compression procedure) to a target hardness of from about 49.03 N to about 78.45 N (about 5.0 to about 8.0 kp) and a friability of from about 0 to about 1 %.

[0027] The several ingredients and some typical replacements for them are as follows:
Mannitol can be used as a natural sweetener. It can be replaced by dextrose, fructose, sorbitol, compressible sugar, or lactose.

[0028] Artificial sweeteners, such as aspartame and saccharin, can be used in combination with natural sweeteners.

[0029] Any pharmaceutically acceptable flavoring agent, natural, artificial, or mixtures thereof, is suitable for use in the dosage form.

[0030] The lubricant can be colloidal silicon dioxide, magnesium stearate, stearic acid, talc, calcium stearate, zinc stearate, leucine, glycerides, sodium stearyl fumarate, or combinations thereof.

[0031] The examples below set forth the ingredients and proportions for typical laboratory scale preparation.

Example 1

[0032] Chewable children's tablets with cough suppressant were prepared. The formulations in unit weight (mg/tablet) and batch weight (gram/preparation) are presented below in Table I. In this example, the analgesic utilized was acetaminophen. The decongestant was pseudoephedrine HCl (PE) and the antihistamine was chlorpheniramine maleate (CM). The cough suppressant dextromethorphan HBr was utilized in the form of 10% (wt) adsorbate.

TABLE I

Ingredients	Unit wt. (mg)
Acetaminophen USP (Powdered)	80.0
Dextromethorphan HBr 10% (Adsorbate)	25.0
Pseudoephedrine HCl USP	7.5
Chlorpheniramine Maleate USP	0.5
Hydroxypropyl Methylcellulose 2910 USP	0.5
Purified Water USP	-
Rotor Coating	
Rotogranulated Actives	113.25
Acetone NF	(113.25)
Eudragit® E 100	5.41
Cellulose Acetate NF, 398-10	10.04
Blending and Compression	
Dye Blend	
Mannitol USP (Granular, FL-2080)	72.00
Aspartame NF	6.57
Colorant	0.039
Mannitol USP (Granular, FL-2080)	229.84
Stearic Acid NF	4.80

TABLE I (continued)

Ingredients	Unit wt. (mg)
Blending and Compression	
Dye Blend	
Colloidal Silicon Dioxide NF	2.40
Actives Granulation	123.79
Flavor	4.56
Microcrystalline Cellulose NF, Avicel PH101	36.00
Total	480.0

[0033] The CM was dissolved in the purified water, PE was added, followed by HPMC, to form the granulating solution, which contained about 70% (wt.) of water. A Glatt GRG-200 rotor granulator was then charged with the acetaminophen and dextromethorphan HBr adsorbate, in that order. The granulating solution was sprayed onto the fluidized acetaminophen and dextromethorphan HBr adsorbate particles and additional purified water was added as necessary to achieve the desired particle size the rotor granulation was then dried and sieved. MM/MAE was dissolved in acetone in a stainless steel container, and cellulose acetate was added to this mixture to form a polymer solution. The ratio of MM/MAE to cellulose acetate was 35:65. The rotor granulator was then charged with the actives granulation and coating was performed. Rotor granules were about 12% (wt.) coated upon completion of the coating process and utilized of the materials listed in Table I. Coated particles were then dried and sieved.

[0034] Blending and compression were then performed in the usual manner. A dye blend was prepared using a portion of the mannitol, aspartame, and colorant. The dye blend was then combined with the coated particles, stearic acid, colloidal silicon dioxide, the remaining mannitol, flavoring, and microcrystalline cellulose to form a final blend. The final blend was then compressed to achieve a final tablet weight of 480 mg. Tablets so produced have a diameter of 10.3 mm (13/32 inch), hardness of from about 49.03 N to about 98.06 N (about 5 to about 10 kp), friability of from about 0 to about 1 %, and thickness of from about 4.5 to about 5 mm.

Example 2

[0035] The same procedure as in Example 1 was carried out, using dextromethorphan HBr in place of the 10% adsorbate. The formulation is presented in Table II below.

TABLE II

Ingredient	Formulation mg/tab
Rotor Granulation	
Acetaminophen USP	80.0
Chlorpheniramine Maleate USP	0.5
Pseudoephedrine HCl USP	7.5
Dextromethorphan HBr (10% adsorbate)	-
Dextromethorphan HBr	2.5
Hydroxypropyl Methylcellulose 2910 USP	0.5
Purified Water USP	(-)
Rotor Coating	
Actives Granulation	91.0
Cellulose Acetate NF 398-10	8.1
Eudragit® E-100	4.3
Acetone NF	(91.0)

TABLE II (continued)

Ingredient	Formulation mg/tab
Blending and Compression	
Aspartame NF	6.6
Colorant	0.04
Mannitol USP (Granular,FL-2080)	322.2
Colloidal Silicon Dioxide NF	2.4
Stearic Acid NF	4.8
Actives Granulation (Coated)	103.4
Flavor	4.6
Microcrystalline Cellulose NF (Avicel PH101)	36.0
Total	480.0

Example 3

[0036] The same procedure as in Example 1 is followed, without any dextromethorphan HBr. The formulation is presented in Table III below.

TABLE III

Ingredient	Formulation mg/tab
GRANULATION	
Acetaminophen USP	80.0
Chlorpheniramine Maleate USP	0.5
Pseudoephedrine HCl USP	7.5
Hydroxypropyl Methylcellulose 2910 USP	0.5
ROTOR COATING	
Actives Granulation	88.5
Cellulose Acetate NF 398-10	7.9
Eudragit® E-100	4.2
Acetone NF	(100.6)
BLENDING AND COMPRESSION	
Aspartame NF	11.0
Colorant	0.66
Mannitol USP (Granular, FL-2080)	318.4
Colloidal Silicon Dioxide NF	2.4
Stearic Acid NF	4.8
Magnesium Stearate NF	-
Actives Granulation	100.6
Citric Acid USP (Anhydrous Powder)	3.1
Flavors	3.1
Microcrystalline Cellulose NF (Avicel PH101)	36.0
Total	480.0

[0037] Other components may be added to the tablets including additional actives, various flavorings, preservatives and other pharmaceutical excipients.

[0038] Application of the compositions and processes of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently and prospectively known to those skilled in the art.

Claims

1. A chewable tablet comprising coated granules compressed with sweeteners, flavoring, and other excipients, said granules individually comprising a solid analgesic, at least one water soluble medicament, and a binder, wherein the coating on said granules comprises a taste-masking composition.

2. The chewable tablet of claim 1, wherein said analgesic is acetaminophen.

3. The chewable tablet of claim 1 or claim 2, wherein said at least one water soluble active is an antihistamine, a decongestant, a cough suppressant or a combination thereof.

4. The chewable tablet of claim 3, which comprises an antihistamine and a decongestant, preferably in combination with a cough suppressant.

5. The chewable tablet of claim 4, comprising acetaminophen, chlorpheniramine, pseudoephedrine and dextromethorphan, or salts thereof, preferably comprising acetaminophen in a dosage of from 80 to 500 mg, chlorpheniramine maleate in a dosage of from 0.5 to 2 mg, pseudoephedrine HCl in a dosage of from 7.5 to 30 mg, and dextromethorphan HBr in a dosage of from 5 to 15 mg.

6. A process for producing a chewable tablet comprising a solid analgesic and at least one water soluble medicament comprising the steps of:

   a) fluidizing a solid analgesic;
   b) spraying a granulating solution comprising said at least one water soluble medicament and a binder onto said fluidized solid analgesic to form an actives granulation;
   c) drying said actives granulation;
   d) coating said actives granulation with a taste-masking composition to form coated granules;
   e) blending said coated granules with sweeteners, flavors, and other excipients; and
   f) compressing to form a tablet.

7. The process of claim 6, further comprising the step of fluidizing a cough suppressant with said solid analgesic.

8. The process of claim 6 or claim 7 which is used to produce a chewable tablet of any one of claims 1 to 5.

Patentansprüche

1. Kautablette, welche umhüllte Granülen umfaßt, die mit Süßstoffen, Geschmacksstoffen und anderen Hilfsstoffen verpreßt sind, wobei die Granülen jede für sich ein festes Analgetikum, wenigstens ein wasserlösliches Arzneimittel und ein Bindemittel umfassen, wobei die Umhüllung um die Granülen eine geschmacksmaskierende Zusammensetzung umfaßt.

2. Kautablette nach Anspruch 1, dadurch gekennzeichnet, daß das Analgetikum Acetaminophen ist.

3. Kautablette nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß der wenigstens eine wasserlösliche Wirkstoff ein Antihistaminikum, ein Dekongestivum, ein Hustenstiller oder eine Kombination derselben ist.

4. Kautablette nach Anspruch 3, dadurch gekennzeichnet, daß sie ein Antihistaminikum und ein Dekongestivum umfaßt, vorzugsweise in Kombination mit einem Hustenstiller.

5. Kautablette nach Anspruch 4, dadurch gekennzeichnet, daß sie Acetaminophen, Chlorpheniramin, Pseu-

doephedrin und Dextromethorphan oder Salze derselben umfaßt, wobei sie vorzugsweise Acetaminophen in einer Dosis von 80 bis 500 mg, Chlorpheniraminmaleat in einer Dosis von 0,5 bis 2 mg, Pseudoephedrin-HCl in einer Dosis von 7,5 bis 30 mg und Dextromethorphan-HBr in einer Dosis von 5 bis 15 mg umfaßt.

6. Verfahren zur Herstellung einer Kautablette, die ein festes Analgetikum und wenigstens ein wasserlösliches Arzneimittel umfaßt, wobei das Verfahren die Schritte umfaßt:

a) Fluidisieren eines festen Analgetikums;

b) Aufsprühen einer Granulationslösung, die das wenigstens eine wasserlösliche Arzneimittel und ein Bindemittel umfaßt, auf das fluidisierte feste Analgetikum, um eine Wirkstoffgranulation zu bilden;

c) Trocknen der Wirkstoffgranulation;

d) Umhüllen der Wirkstoffgranulation mit einer geschmacksmaskierenden Zusammensetzung, um umhüllte Granülen zu bilden;

e) Vermischen der umhüllten Granülen mit Süßstoffen, Geschmacksstoffen und anderen Hilfsstoffen; und

f) Verpressen, um eine Tablette zu bilden.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß es außerdem den Schritt der Fluidisierung eines Hustenstillers mit dem festen Analgetikum umfaßt.

8. Verfahren nach Anspruch 6 oder Anspruch 7, dadurch gekennzeichnet, daß es verwendet wird, um eine Kautablette nach einem der Ansprüche 1 bis 5 herzustellen.

Revendications

1. Comprimé à croquer comprenant des granules enrobés comprimés avec des édulcorants, des aromatisants et d'autres excipients, lesdits granules comprenant individuellement un analgésique solide, au moins un médicament soluble dans l'eau, et un liant, dans lequel l'enrobage sur lesdits granules comprend une composition de masquage du goût.

2. Comprimé à croquer selon la revendication 1, dans lequel ledit analgésique est l'acétaminophène.

3. Comprimé à croquer selon la revendition 1 ou 2, dans lequel ledit au moins 1 principe actif soluble dans l'eau est un antihistaminique, un décongestionnant, un sédatif de la toux ou une de leurs combinaisons.

4. Comprimé à croquer selon la revendication 3, qui comprend un antihistaminique et un décongestionnant, de préférence en combinaison avec un sédatif de la toux.

5. Comprimé à croquer selon la revendication 4, comprenant l'acétaminophène, la chlorphéniramine, la pseudoéphédrine et le dextrométhorphane, ou leurs sels, comprenant de préférence l'acétaminophène à une dose de 80 à 500 mg, la chlorophéniramine maléate à une dose de 0,5 à 2 mg, la pseudoéphédrine HCl à une dose de 7,5 à 30 mg et le dextrométhorphane HBr à une dose de 5 à 15 mg.

6. Procédé pour la production d'un comprimé à croquer comprenant un analgésique solide et au moins un médicament soluble dans l'eau, qui comprend les étapes qui consistent à :

a) fluidiser un analgésique solide ;
b) pulvériser une solution de granulation comprenant ledit au moins 1 médicament soluble dans l'eau et un liant sur ledit analgésique solide fluidisé pour former des granules actifs;
c) sécher lesdits granules actifs ;
d) enrober lesdits granules actifs avec une composition de masquage du goût pour former les granules enrobés ;
e) mélanger lesdits granules enrobés avec des édulcorants, des aromatisants et d'autres excipients ; et

f) comprimer pour former un comprimé.

7. Procédé selon la revendication 6, qui comprend en outre l'étape qui consiste à fluidiser un sédatif de la toux avec ledit analgésique solide.

8. Procédé selon la revendication 6 ou 7, qui est utilisé pour produire un comprimé à croquer selon l'une quelconque des revendications 1 à 5.